§112, first paragraph, for the same reason. Applicants respectfully traverse this rejection.

The enablement requirement refers to the requirement of 35 U.S.C. §112, first paragraph, that the specification describe how to make and how to use the invention. As mandated by MPEP §2164, the invention that one skilled in the art must be enabled to make and use is that **defined by the claims** of the particular application or patent. The claims of the instant application are drawn to a method of delivering a selected DNA sequence to the central nervous system of a mammal comprising administering a neurotropic viral vector capable of infecting the central nervous system of a mammal, said vector containing a selected DNA sequence, said sequence being operatively linked to a selected promoter. There is no limitation in the claim that the host must receive a benefit from the method of delivery. Accordingly, the Examiner's requirement that a benefit be demonstrated is unwarranted in light of the claim language.

Further, the Examiner has provided no reasonable basis for questioning the ability of the instant invention to deliver a gene to the central nervous system such that the host would receive a benefit from such delivery. As mandated by MPEP §2164.04, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993) wherein

the CAFC held that the Examiner must provide a reasonable explanation as to why the scope of the protection provided by a claim is not adequately enabled by the disclosure. As stated by the Court in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971),

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent wit the contested statement. Otherwise, there is no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. 169 USPQ at 370.

The Examiner has provided so such explanation, evidence or reasoning in the instant case.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. As acknowledged by the Examiner, Applicants have shown that the biologically active molecule, β-glucuronidase is expressed in the central nervous system when the DNA sequence encoding this molecule is operatively linked to the LAT promoter contained in the neurotropic virus, HSV. Examples of other

neurotropic viruses which can serve as vectors in the present invention are disclosed at pages 10 and 11. The Examiner suggests that Applicants have not provided evidence that other neurotropic viruses would reach the CNS. By definition, however, neurotropic viruses must be capable of infecting the central nervous system (CNS) of a mammal. See page 10 of the instant specification. Accordingly, there is no reasonable basis for requiring evidence of this ability.

The Examiner also suggests that Applicants have not shown that neurotrophic viruses would reach the CNS by other routes of delivery. Various routes of delivery are disclosed in the specification are page 20 and include corneal scarification, intranasal exposure and foot-pad injection which lead to infection of neurons of the trigeminal ganglion, the olfactory system, and the cervical ganglion, respectively. The virus may also be delivered by injection through a spinal tap into the cerebrospinal fluid, or by infection into any tissue where the virus might gain access to the nervous system. However, the Examiner suggests that the blood brain barrier may be "problematic" with regard to "systemic delivery". Further, the Examiner suggests that evidence has not been presented that HSV will infect CNS by other routes of delivery. It is respectfully pointed out, however, that the ability of neurotrophic viruses to infect the CNS was known in the art. As taught in the specification at page 5 infection with

herpes simplex virus (HSV-1), a neurotropic virus, begins with viral replication in epithelial tissues. After initial replication at the site of infection, HSV-1 establishes latent infection in the nervous system during which no virus can be detected unless reactivation occurs. It was known in the prior art that during latency viral DNA can be detected in the CNS of mice and humans. See specifically, Fraser et al., "Molecular biology of latent HSV-1. In: Human herpes virus infections. II viral glycoproteins and immunobiology", Raven Press NY 39-55 (1986) cited in the specification and provided in the Information Disclosure Statement. Accordingly, one of skill in the art would have no reason to doubt the objective truth of teachings provided in the specification regarding various routes of delivery. Thus, again there is no basis for the Examiner's requirement for additional evidence of efficacy.

The Examiner has clearly failed to meet the burden of establishing a reasonable basis to question the enablement provided for the claimed invention. Accordingly, withdrawal of the objection to the specification and rejection of claims 1-9 under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Examiner also suggests that Applicants have not provided any evidence of promoters other than the LAT promoter which would be effective in the claimed methods. The Examiner suggests that for sustained expression, it would seem that latency or a non-

reproductive cycle would need to be established. Accordingly, in an earnest effort to advance the prosecution, Applicants have amended claim 1 to be drawn to a method wherein the promoter is capable of expressing the selected DNA sequence during a latent infectious state. Withdrawal of the objection to the specification and rejection of claims 1-9 under 35 U.S.C. §112, first paragraph, is, therefore, respectfully requested.

**II. Rejection of Claims 1, 2, 5 and 6 under 35 U.S.C. §102(b)**

Claims 1, 2, 5 and 6 have been rejected under 35 U.S.C. §102(b) as being clearly anticipated by Dobson et al. (1989) J. Virol. 63, 3844-3851. Applicants respectfully traverse this rejection.

To anticipate a claim, the reference must teach every element of the claim. See MPEP §2131. The claims of the instant invention are drawn to a method of delivering a selected DNA sequence to the central nervous system of a mammal comprising administering a neurotropic viral vector capable of infecting the central nervous system of a mammal, said vector containing a selected DNA sequence, said sequence being operatively linked to a selected promoter. In contrast, Dobson et al. demonstrate that insertion of the rabbit beta-globin gene into HSV immediately downstream of a potential Pol II promoter sequence of 700 bases 5' of the start of the stable nuclear poly A LAT results in the expression of cytoplasmic

poly(A)+ globin RNA in lumbosacral spinal ganglia. However, as clearly taught in the specification at page 7, the spinal ganglia are part of the peripheral nervous system, not the central nervous system. Accordingly, this reference does not teach every element of the claims and therefore does not anticipate the instant invention. It is, therefore, respectfully requested that this rejection be withdrawn.

**III. Rejection of Claims 3, 4, 7, 8 and 9 under 35 U.S.C. §103**

Claims 3, 4, 7, 8 and 9 have been rejected under 35 U.S.C. §103 as being unpatentable over Dobson et al. (1989) *J. Virol.* 63, 3844-3851 in view of Nishimura et al. (1986) *Proced. Nat'l Acad. Sci.* 83, 7292-7296. Applicants respectfully traverse this rejection.

Contrary to the Examiner's suggestion, Dobson et al. do not teach the delivery of the rabbit beta-globin gene to the CNS of mice. As discussed in Section II, *supra*, Dobson et al. demonstrate the delivery of this gene to the spinal ganglia which is part of the peripheral nervous system, not the central nervous. Accordingly, the Examiner's basis for this rejection is flawed. Further, nowhere in the disclosure by Dobson et al. is there any suggestion or teaching that the rabbit β-globin gene can be replaced with a selected DNA sequence encoding a compound which alters a neurological function. In fact, the inclusion of the β-

globin gene merely served as a reporter to monitor and study the latency-associated transcript promoter. There is also no suggestion that the latency-associated transcript promoter could serve as a means for delivering a DNA sequence capable of altering a neurological function. Thus, Dobson et al. provide no suggestion to one of ordinary skill in the art to make the invention of the present application which render the present invention obvious.

The Examiner suggests that Dobson et al. provide one of skill with the motivation to make the instant invention in the 3rd paragraph of column to at page 2850. This states that:

> there is considerable interest in using HSV-1 as a vector for gene transfer to neurons. The beta globin virus used in these experiments fairly faithfully expressed a foreign gene product stably in neurons in vivo. The lack of expression of HSV-1 in latent neurons may make this an attractive system.

Clearly, this paragraph at most provides a motivation to try to make to make a vector such as that used in the method of the instant invention. However, the CAFC has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure. However, to render an invention obvious under §103, there must be both suggestion and reasonable expectation of success founded in the prior art. There is simply no such suggestion or teaching in

the Dobson reference. Nor does the reference by Nishimura et al., cited by the Examiner merely for teaching the DNA sequence for β-glucuronidase, provide the necessary details to render the instant invention obvious.

In cases where it was decided that the prior art did contain a suggestion of the invention and a reasonable expectation of success, such as *In re O'Farrell*, 853 F.2d 892 (Fed. Cir. 1988), the prior art contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful. The combination of Dobson et al. and Nishimura et al. simply does not contain these elements. Accordingly, the rejection of claims 3, 4, 7, 8 and 9 under 35 U.S.C. §103 is improper. It is, therefore, respectfully requested that this rejection be withdrawn.

**IV. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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